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Risk Factors Related to Locoregional Recurrence in Squamous Cell Carcinoma of the Skin

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A retrospective analysis was performed to identify the risk factors associated with development of locoregional recurrent disease in patients with primary squamous cell carcinoma of the skin. Step-wise logistic regression analysis was used in this study, which consisted of 1,039 patients treated from January 1980 to December 1989 at Ankara Oncology Hospital. Locoregional recurrence occurred in 187 (18%) of these patients within a mean disease-free period of 15 months. Age, sex, anatomical location, size of lesion, lymph node status at diagnosis, stage according to TNM classification, histopathologic grade, previous therapy, treatment modality, lesions arising from scar tissue (scar carcinoma), regional lymph node dissection, concomitant premalignant tumor of the skin, development secondary nonmelanotic skin carcinoma, and second malignancy were used as variables that could be correlated with locoregional recurrent disease. No correlation was found between development of recurrence and previous therapy, second nonmelanoma skin cancer, second malignancy, premalignant skin tumor, sex, or regional lymph node dissection. Although univariate analysis demonstrated that location, tumor size, patient's age, lymph node status, stage, histopathologic grade, scar carcinoma, and treatment modality were associated with an increased risk of locoregional recurrence, it was found that stage of the disease ($P < 0.001$), treatment modality ($P < 0.01$), tumor arising from scar tissue ($P < 0.01$), and histopathologic grade ($P < 0.05$) were statistically significant as risk factors of recurrence when a multivariate analysis was applied.

KEY WORDS: **skin, epidermoid cancer, recurrent disease**

INTRODUCTION

According to many reported studies [1–5], nonmelanotic skin carcinomas are the most common cancers among white-skinned people. Squamous cell carcinoma (SCC) of the skin is seen less frequently than basal cell carcinoma (BCC) and usually occurs among the elderly. Although it mostly appears on sun-exposed areas in fair-skinned people, it is reported that tumors developing from scar tissues such as burns and traumas tend to have more aggressive behavior [6–10]. The local or regional recurrence rate of SCC ranges from 0.5% to 58% in the published data [8,9,11–15].

This study identifies the incidence of locoregional recurrence and investigates risk factors that can be related to locoregional recurrent disease in patients with SCC.

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MATERIALS AND METHODS

From January 1980 to December 1989, 3,749 consecutive patients with nonmelanotic skin cancer, excluding the anogenital region and mucocutaneous sites, were treated at Ankara Oncology Hospital. During this period, 1,283 of these patients were diagnosed with primary SCC of the skin. All medical records were reviewed retrospectively. A total of 154 patients were not included in this study because of inadequate follow-up data, and 90 patients were excluded from the analysis because of insufficient data related to tumor size.

Risk factors that can be correlated with local and/or regional recurrence were examined in 1,039 remaining patients. Age, sex, anatomical site of the primary lesion, histopathologic grade, primary tumor size (T), regional lymph node status at diagnosis (N), stage according to TNM classification of American Joint Committee on Cancer (AJCC)-1988, lesion arising from scar tissue, prior to any treatment history, treatment modality, regional lymph node dissection, concomitant premalignant tumor of the skin, development of metachronous or synchronous nonmelanotic skin cancer, and second malignancy during follow-up, were used as variables for the analysis.

Statistical Methods

The Chi-square statistic, uncorrected for continuity, was used to test for statistically significant differences between proportions of patients showing recurrence and, where appropriate, to test for linear trend. In general, the Chi-square test was considered to be significant at the $P = 0.05$ level; otherwise, it was reported as insignificant. To examine the effects on locoregional recurrence of more than one risk factor simultaneously, a stepwise logistic regression analysis was performed in the study. Backward elimination was used, starting with all potential risk factors. All the variables that could be associated with locoregional recurrence were examined independently in two groups in the multivariate study: namely, Model I (including TNM classification) and Model II (excluding stage). Statistical analysis was performed by 4F,2D,LR of BMDP/Dynamic release 7 (BMDP statistical software). In addition, a standard spreadsheet (Lotus 123) was applied to determine the relative importance of risk factors that were found in the multivariate analysis according to Model I.

RESULTS

Patient Population

Locoregional recurrent disease with a median follow-up of 28 months (range: 6–149 months) developed in 187 (18%) of 1,039 patients. There was local and regional recurrence in 17 patients, whereas local recurrence and regional metastases alone developed in 150 and 20 patients, respectively. The mean time period between treatment of primary SCC and development of locoregional recurrence was 15 months with a range of 1–99 months. Of all the locoregional recurrent diseases, 75% appeared within 16 months. The age at diagnosis of 1,039 patients varied from 15 to 97 years. The mean age was 60.6 ± 13.1 (median age: 65 years). There were 670 men and 369 women (male-to-female ratio: 1.8/1).

TABLE I. Factors Not Statistically Significant on Locoregional Recurrence by Univariate Analysis in 1,039 Patients With Squamous Cell Carcinoma of the Skin

Variable	% Recurring (r/n)[a]	*P* value*
Previous therapy		
No	17.7 (173/977)	0.3327
Yes	22.6 (14/62)	
Lymph node dissection		
No	18.2 (182/999)	0.3560
Yes	12.5 (5/40)	
Second nonmelanoma skin cancer		
No	18.5 (172/930)	
Basal cell carcinoma	10.9 (5/46)	0.3806
Squamous cell carcinoma	15.9 (10/63)	
Second malignancy		
No	18.0 (184/1021)	0.8821
Yes	16.7 (3/18)	
Concomitant premalignant skin disease		
No	18.2 (183/1004)	0.3034
Yes	11.4 (4/35)	
Sex		
Male	18.8 (126/670)	0.3610
Female	16.5 (61/369)	

[a] r = number of patients with recurrent disease; n = number of all patients.
* *P* value of Chi-square test.

The patients were identified in eight distinct groups according to the anatomical site of the lesions: face (372 patients), nose (173), ear (162), upper limb (143), lower limb (90), scalp (46), trunk (35), eyelid (18 patients). Medical records disclosed that 62 of these patients with primary SCC had undergone prior treatments that included topical therapy or electrodesiccation.

SCC arising from scar tissues were seen in 61 patients. Most of these were due to burns in childhood. Interestingly, in only one patient did the lesion develop from the scar tissue associated with favus in scalp. In two patients, SCC arose from scars related to trauma.

All the patients were categorized into stage by TNM classification of AJCC-1988. The patient distribution according to primary tumor in its largest dimension were as follows: tumor 2 cm or less in greatest dimension (T1) in 472 patients; tumor >2 cm but not >5 cm (T2) in 359; tumor size >5 cm (T3) in 135; and tumor invaded deep extradermal structures (T4) in 73 patients. Twenty patients were found to have clinically or histopathologically regional lymph node metastasis (N1) at the time of diagnosis. Accordingly, there were 469 patients in Stage I (T1N0M0), 483 in Stage II (T2N0M0 in 350, T3N0M0

in 133), and 87 patients in Stage III (T4N0M0 in 67, T1N1M0 in 3, T2N1M0 in 9, T3N1M0 in 2, T4N1M0 in 6).

The degree of histologic differentiation of each tumor was indicated by a pathology report. Thus there was well-differentiated tumor (G1) in 466 patients, moderately well differentiated (G2) in 127, poorly differentiated (G3) in 38, and undifferentiated tumor (G4) in 23 patients. The lesions that could not be assessed for grading (Gx) were found in the remaining patients. In addition, it was seen that 35 patients had a concomitant premalignant condition including keratoacanthoma, xeroderma pigmentosum, and actinic or solar keratosis. Metachronous or synchronous secondary SCC of the skin occurred in 46 patients and BCC of the skin in 63 patients. Second malignancy (lung, parotid gland, lip, larynx tumors) at follow-up developed in 18 patients.

Regional lymph node dissection was added in 40 of 885 patients who underwent surgical therapy. Of those, 50% were found to have histopathologically lymph node metastases.

Fifty-six patients who were subjected to amputation underwent different amputations of upper or lower limbs, and 39 patients with SCC in the ear underwent a total resection of the auricle because large lesions on the entire auricle and those involving deep tissue required more extensive surgery. Generally, a skin graft (free or composite grafts) or a random pattern flap (rotation or transposition) has been used for reconstruction of wide cutaneous defects after surgical wide excision with adequate margins.

Univariate Analysis

Among 14 variables used in the statistical analysis, no significant statistical differences were found in the six variables: previous therapy, regional lymph node dissection, concomitant premalignant skin lesions, sex, second nonmelanoma skin cancer (SCC, BCC), and second malignancy at follow-up ($P > 0.05$). The distribution of these is listed in Table I.

Lesions located on the eyelid were associated with a decreased risk of recurrence, whereas those on the nose, ear, trunk, limb, scalp, and face yielded an increased risk of recurrent disease ($P < 0.05$). Patients with tumors of 2 cm or less had less frequent risk of recurrence compared to those with T2, T3, and T4 ($P < 0.0001$). The increased recurrence rate also was found in patients who had regional lymph node metastasis ($P < 0.002$). Thus locoregional recurrence occurred more frequently in patients with an advanced stage than those with Stage I ($P < 0.0001$). Whereas well-differentiated tumors carried the lowest risk, the highest rate of recurrence was seen among patients with undifferentiated tumors ($P < 0.005$). In addition, significant association with recurrence was found among patients <40 years of age compared to those >40 years of age ($P < 0.05$). The greater probability of recurrence also was seen among the lesions that arose from scar tissue ($P < 0.001$). Patients who were treated only with radiotherapy or chemotherapy or both were found to have an increased risk of recurrence.

Amputation was not superior to surgical total excision

TABLE II. Risk Factors for Locoregional Recurrence by Univariate Analysis Among 1,039 Patients With Squamous Cell Carcinoma of the Skin

Variable	% Recurring (n/r)[a]	*P* value*
Anatomical site		
Trunk	28.6 (10/35)	
Nose	12.7 (22/173)	
Ear	13.6 (22/162)	
Eyelid	5.6 (1/18)	0.0498
Face	20.6 (76/372)	
Scalp	19.6 (9/46)	
Upper limb	17.5 (25/143)	
Lower limb	24.5 (22/90)	
Primary tumor size (T)[b]		
T1	10.4 (49/472)	
T2	20.9 (75/359)	
T3	31.9 (43/135)	0.0000
T4	27.4 (20/73)	
Lymph node status (N)		
No	17.5 (178/1019)	0.0015
N1	45.0 (9/20)	
Histopathologic grade (G)		
Gx	17.9 (69/385)	
G1	14.6 (68/466)	
G2	25.2 (32/127)	
G3	23.7 (9/38)	0.0031
G4	39.1 (9/23)	
Stage[b]		
Stage I	10.0 (47/469)	
Stage II	23.4 (113/483)	0.0000
Stage III	31.0 (27/87)	
Age		
<40	30.0 (15/50)	0.0236
≥40	17.4 (172/989)	
Lesion arising from scar tissue		
No	16.9 (165/978)	0.0002
Yes	36.1 (22/61)	
Treatment modality[c]		
Local excision	15.7 (87/554)	
Local excision + RT	12.6 (26/206)	
Local excision + CT	11.1 (2/18)	
Local excision + RT + CT	8.3 (1/12)	
Amputation + RT	23.8 (5/21)	
Amputation + CT	10.0 (1/10)	0.0001
Amputation	21.9 (14/64)	
RT + CT	42.9 (9/21)	
RT	31.4 (37/118)	
CT	33.3 (5/15)	

[a] r = number of patients with recurrent disease; n = number of all patients.
[b] Linear trend test was used in addition to Pearson Chi-square.
[c] RT = radiotherapy; CT = chemotherapy.
* *P* value of Chi-square test.

TABLE III. Level of Significance of All Variables Used in Statistical Analysis for Locoregional Recurrence of Squamous Cell Carcinoma of the Skin

Variable	Univariate analysis (Chi-square test) (P value)	Multivariate analysis (stepwise logistic regression) Model I (P value)	Model II (P value)
Previous therapy	0.3327	0.2965	0.3023
Treatment modality	0.0001***	0.0069**	0.0182*
Lymph node dissection	0.3560	0.3009	0.2219
Second nonmelanoma skin cancer	0.3806	0.9211	0.9272
Anatomical site	0.0498*	0.6216	0.5418
Second malignancy	0.8821	0.8746	0.8220
Concomitant premalignant skin lesion	0.3034	0.6215	0.5941
Sex	0.3610	0.4299	0.4088
Primary tumor size (T)	0.0000***	0.2509	0.0005***
Lymph node status (N)	0.0015**	0.3134	0.0348*
Histopathologic grade (G)	0.0031**	0.0152*	0.0191*
Stage	0.0000***	0.0000***	—
Age	0.0236*	0.2382	0.2548
Lesion arising from scar tissue	0.0002***	0.0022**	0.0094**

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

with adequate margins. Patients treated with adjuvant radiotherapy and chemotherapy following total excision showed the lowest recurrence rate. The analysis of risk factors related to locoregional recurrence by the univariate method is shown in Table II.

Multivariate Analysis

Stepwise logistic regression analysis was applied to the factors that were found to have a significant influence on locoregional recurrence based upon the aforementioned univariate analysis. In principal, multivariate analysis according to Model I (including stage) was taken into consideration because disease stage should not be excluded. Thus four factors related to recurrence remained: stage, histopathologic grade, treatment modality, and pre-existing scar tissue. The level of significance of the factors evaluated by univariate and multivariate analysis is listed in Table III. It was seen that patients with an advanced stage had a higher risk of developing locoregional recurrent disease ($P < 0.0001$). Tumors arising from scar tissue were significantly correlated with an increased risk of recurrence ($P < 0.01$). Besides, the multivariate method confirmed that histopathologic grade ($P < 0.05$) and type of primary treatment ($P < 0.05$) were also significantly associated with the risk of recurrence (Table IV). Patient age at diagnosis, tumor location, tumor size, and lymph node status did not make any significant differences to the recurrence according to the results of this analysis ($P > 0.05$).

The relative importance of risk factors could be compared by standardized coefficients [16]. Although four important risk factors were well established in terms of Model I multivariate study, in order to identify the most important of the four main risk factors, standardized coefficients were applied to the findings of the stepwise logistic regression analysis. In regard to this, an advanced stage was seen to be the most important risk factor for recurrence in our series. Other factors were in order as follows: stage II disease; treatment with X-ray, grade 2 tumor, scar carcinoma, receiving chemotherapy and radiotherapy, and grade 4 tumor (Table V).

DISCUSSION

SCC of the skin is known to have a low rate of recurrence. Abbatucci et al. [14] reported that the incidence of recurrence was 2.8% and that all the recurrences appeared within 2.5 years. Immerman et al. [11] also pointed out a 19.8% of locoregional recurrence rate in patients with invasive SCC. Their series demonstrated that the larger, less differentiated, and Clark's Level IV or V lesions had an increased rate of recurrence. In our study, 18% of recurrence was seen within a mean period of 15 months in 1,039 patients with SCC. When the univariate analysis was applied to determine the risk factors, eight of these were found to have influence among 14 variables that could be correlated with a probability of recurrence. However, to be able to obtain useful information, these findings should be confirmed by multivariate study because univariate methods could not produce clear results. Therefore significant associations with recurrence were found in only four factors.

It has been suggested that scar carcinoma was an aggressive tumor with a high potential for recurrence and metastases. Some studies reported that SCC arising from scars carried a worse prognosis than tumor arising from unscarred skin, regardless of the cause of scar [8,9,17]. This poor prognosis was caused by low immunocompetence [17]. In this study, multivariate analysis

TABLE IV. Squamous Cell Carcinoma of the Skin: Results of Stepwise Logistic Regression Analysis (According to Models I & II)

	Model I (including TNM stage)			Model II (excluding TNM stage)		
		95% Confidence interval of odds ratio			95% Confidence interval of odds ratio	
Variable	Odds ratio	Minimum	Maximum	Odds ratio	Minimum	Maximum
Treatment modality[a]						
Local excision (n = 554) (Reference category)						
Local excision + RT (n = 206)	0.98	0.59	1.60	0.99	0.60	1.62
Local excision + CT (n = 18)	0.50	0.11	2.28	0.48	0.10	2.22
Local excision + RT + CT (n = 12)	0.31	0.04	2.62	0.34	0.41	2.82
Amputation + RT (n = 21)	1.00	0.32	3.19	1.09	0.34	3.48
Amputation + CT (n = 10)	0.22	0.03	1.96	0.18	0.18	1.73
Amputation (n = 64)	0.64	0.27	1.49	0.70	0.29	1.70
RT + CT (n = 21)	3.31[b]	1.29	8.49	3.06[b]	1.17	7.98
RT (n = 118)	2.27[b]	1.37	3.74	2.20[b]	1.33	3.65
CT (n = 15)	1.44	0.41	5.04	1.45	0.42	5.02
Histopathologic grade (G)						
G1 (n = 466) (Reference category)						
Gx (n = 385)	1.04	0.70	1.56	1.06	0.71	1.58
G2 (n = 127)	2.06[b]	1.25	3.38	2.09*	1.27	3.43
G3 (n = 38)	1.40	0.60	3.25	1.31	0.55	3.13
G4 (n = 23)	2.73[b]	1.08	6.93	2.54*	0.98	6.55
Stage						
Stage I (n = 469) (Reference category)						
Stage II (n = 483)	2.19[b]	1.48	3.24			
Stage III (n = 87)	4.43[b]	2.02	9.72			
Tumor size (T)						
T1 (n = 472) (Reference category)						
T2 (n = 359)				1.93[b]	1.28	2.90
T3 (n = 135)				2.64[b]	1.54	4.53
T4 (n = 73)				3.60[b]	1.50	8.62
Lymph node status						
No (n = 1019) (Reference category)						
N1 (n = 20)				3.13*	1.09	8.98
Lesion arising from scar tissue						
No (n = 978) (Reference category)						
Yes (n = 61)	2.53[b]	1.40	4.57	2.30*	1.23	4.30

[a]n = number of patients; RT = radiotherapy; CT = chemotherapy.
[b]Coefficient of each risk factor according to reference category in that group.

TABLE V. Squamous Cell Carcinoma of the Skin: Relative Importance of High Risk Factors Established in Terms of Model I Multivariate Analysis According to Standardized Coefficients

Variable	Standard deviation	βI[a]	Standardized coefficient[b]
(1) Stage III disease	0.276989	1.4890	0.412436
(2) Stage II disease	0.498764	0.7840	0.391031
(3) Radiotherapy	0.317289	0.1960	0.259796
(4) Grade 2 tumor	0.327554	0.7209	0.236134
(5) Scar carcinoma	0.235081	0.9283	0.218226
(6) Radiotherapy + chemotherapy	0.140723	0.8183	0.168305
(7) Grade 4 tumor	0.147127	1.0060	0.148010

[a]Regression coefficient.
[b]Standardized coefficient = regression coefficient × standard deviation of variable.

shows that scar carcinoma has a 2.53-fold recurrence risk compared to unscarred carcinoma (Table IV). Moderately well differentiated and undifferentiated tumor is associated with an increased risk of recurrence of 2.06- and 2.73-fold, respectively, compared to well-differentiated tumor. Considering this finding, it could be argued that less differentiated tumor should be treated with multidisciplinary management. In effect, the

TABLE VI. Relationship Between Treatment Modality and Tumor Size (T) Among 1,039 Patients With Squamous Cell Carcinoma of the Skin

Treatment modality	T1[a]	T2	T3	T4	Total
Local excision	428 (90.7%)	262 (73%)	92 (68.1%)	8 (11%)	790 (76%)
Amputation	9 (1.9%)	25 (7%)	5 (3.7%)	56 (76.7%)	95 (9.1%)
Other[b]	35 (7.4%)	72 (20.1%)	38 (28.1%)	9 (12.3%)	154 (14.8%)
Total	472	359	135	73	1,039

[a]Number of patients according to tumor size.
[b]Radiotherapy, chemotherapy, or both.
( ) = percentage of cases.

patients who underwent surgical excision with adjuvant radiotherapy and chemotherapy had the lowest ratio of recurrence in this univariate study. However, the results of interrelation treatment modalities in connection with the multivariate study showed that only radiotherapy and radiotherapy combined with chemotherapy as the initial therapeutic management had higher risk factors (3.31 vs. 2.27) (Table IV).

Despite the fact that no statistical difference was seen between surgical excision and amputation in our study, some reports advocated that amputation should be performed in order to obtain tumor-free margins [8,18,19]. Lifeso et al. [19] advocated that amputation was the procedure of choice for all patients with Grade 2 or 3 tumors. We also have agreed that amputation may be required to achieve local tumor control only if the tumor has fixed or invaded deep extradermal structures such as cartilage or bone, regardless of degree of tumor differentiation. In fact, 76.7% of the patients with T4 tumor in our series underwent amputation, but only 11% were treated with wide local surgical excision (Table VI). Moreover, the majority of patients with T1 tumor (90.7%) were treated with surgical excision, whereas amputation was performed in only 1.9% of T1 tumors. That was probably because there was no statistical difference between two surgical managements in our series.

Elective lymph node dissection (ELND) for cutaneous SCC is still controversial. In this study no statistical significance was found for regional lymph node dissection. Some studies demonstrated that patients with nodal metastases had an increased survival and decreased recurrence rate only if they underwent therapeutic radical regional lymph node dissection or nodal irradiation [8,19]. However, there has been no uniform exact policy of node dissection. Currently we are not in favour of ELND. We have concluded that surgical resection with regional lymph node dissection is an appropriate treatment if the patient has nodal metastases.

The standardized coefficient revealed that patients with stage III disease carried the highest risk of recurrence (Table V). Friedman et al. [12] investigated the rate of recurrence and prognosis in 63 patients with cutaneous SCC of extremities and trunk, excluding head and neck tumors. They suggested that the level of tumor invasion, histological grade, and tumor thickness (microstaging cutaneous SCC) without regard to the TNM staging system may be more useful prognostic variables and more important factors for recurrence, because most patients with SCC of skin have local tumors. They also advocated ELND for tumors that penetrated through the dermis or exceeded 8 mm in thickness. When we applied the stepwise logistic regression analysis, excluding TNM staging system (Model II), it was found that treatment modality, scar carcinoma, histopathologic grade (G), primary tumor size (T), and lymph node status (N) were related to the development of locoregional recurrent disease. These findings are listed in Tables III and IV. In contrast, the multivariate study including TNM classification (Model I) showed that stage was one of the risk factors for recurrence (Table IV). Furthermore, stage III disease was the most important risk factor according to standardized coefficient. Accordingly, patients at an advanced stage yield high recurrence rates.

Some studies reported that patients with recurrent SCC that developed from preexisting scarring carried high rates of recurrent disease, distant metastases, and mortality [8,17,20–22]. But in our series, according to the standardized coefficient, scar carcinoma was a less important factor than advanced disease stage. Although follow-up time of our series was not long enough, this retrospective experience also supported the view that lesions, particularly at advanced stages, should be carefully evaluated and followed after treatment. Moreover, one might argue that surgical management should be preferred instead of radiotherapy or chemotherapy as an initial treatment of primary SCC of the skin.

In general, appropriate initial therapeutic management was determined by how far the disease has progressed during this period. Despite this, location of lesion, patient's age, and socio-economic conditions were among other factors that influenced the choice of treatment. It is interesting to observe that 59.4% of the patients have undergone only surgical therapy, and 25.4% were treated with surgery and adjuvant therapy (RT or CT or both of

them). Whereas local excision alone could be sufficient for local tumors, patients with locally advanced lesions should receive adjuvant therapy in addition to surgery. Generally, radiotherapy or chemotherapy alone is not advised.

CONCLUSION

In this retrospective study, using a stepwise logistic regression analysis, increased risk for the development of locoregional recurrent disease was found to be associated with four factors: stage according to TNM classification, histopathologic grade, treatment modality, and scar carcinoma. It should be emphasized that advanced stage tumors were carefully evaluated because a stage III disease among these factors had a greater probability of recurrence according to standardized coefficients. If possible, radiotherapy alone or radiotherapy combined with chemotherapy should be avoided because of a high recurrence rate. It became clear from our experience that local surgical excision with adequate margins was an appropriate choice of treatment.

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